VOLUME 22 · NUMBER 5 · MARCH 1 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Gefitinib in Combination With Paclitaxel and Carboplatin in Advanced Non–Small-Cell Lung Cancer: A Phase III Trial—INTACT 2

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Submitted July 24, 2003; accepted November 26, 2003.

Supported by a grant from AstraZeneca, Wilmington, DE.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/04/2205-785/$20.00

DOI: 10.1200/JCO.2004.07.215

ABSTRACT

Purpose
Preclinical studies indicate that gefitinib (Iressa, ZD1839; AstraZeneca, Wilmington, DE), an orally active epidermal growth factor receptor tyrosine kinase inhibitor, may enhance antitumor efficacy of cytotoxics, and combination with paclitaxel and carboplatin had acceptable tolerability in a phase I trial. Gefitinib monotherapy demonstrated unparalleled antitumor activity for a biologic agent, with less toxicity than docetaxel, in phase II trials in refractory, advanced non–small-cell lung cancer (NSCLC). This phase III, randomized, placebo-controlled, double-blind trial evaluated gefitinib plus paclitaxel and carboplatin in chemotherapy-naive patients with advanced NSCLC.

Patients and Methods
Patients received paclitaxel 225 mg/m^2 and carboplatin area under concentration/time curve of 6 mg/min/mL (day 1 every 3 weeks) plus gefitinib 500 mg/d, gefitinib 250 mg/d, or placebo. After a maximum of six cycles, daily gefitinib or placebo continued until disease progression. End points included overall survival, time to progression (TTP), response rate (RR), and safety evaluation.

Results
A total of 1,037 patients were recruited. Baseline demographic characteristics were well balanced. There was no difference in overall survival (median, 8.7, 9.8, and 9.9 months for gefitinib 500 mg/d, 250 mg/d, and placebo, respectively; $P = .64$), TTP, or RR between arms. Expected dose-related diarrhea and skin toxicity were observed in gefitinib-treated patients, with no new significant/unexpected safety findings from combination with chemotherapy. Subset analysis of patients with adenocarcinoma who received ≥ 90 days' chemotherapy demonstrated statistically significant prolonged survival, suggesting a gefitinib maintenance effect.

Conclusion
Gefitinib showed no added benefit in survival, TTP, or RR compared with standard chemotherapy alone. This large, placebo-controlled trial confirmed the favorable gefitinib safety profile observed in phase I and II monotherapy trials.

J Clin Oncol 22:785-794. © 2004 by American Society of Clinical Oncology

INTRODUCTION

Lung cancer is the most common cause of cancer death worldwide [1]. Current first-line chemotherapy options for patients with advanced non–small-cell lung cancer (NSCLC), such as the combination of a platinum-based agent with paclitaxel, gemcitabine, vinorelbine, or docetaxel, have substantial toxicity and seem to have reached a plateau in terms of efficacy. A randomized study by the Southwest Oncology Group showed that paclitaxel with carboplatin has similar efficacy to vinorelbine with cisplatin (median survival, 8 months for both regimens; 1-year survival, 38% and 36%, respectively) [2]. More recently, a study by the Eastern Cooperative Oncology Group found that four different platinum-based regimens had similar efficacies [3]. Clearly, improve-

ment on these existing treatments for advanced NSCLC is needed, requiring the development of new agents with a different mechanism of action and an improved safety profile compared with chemotherapy.

The orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib (Iressa, ZD1839; AstraZeneca, Wilmington, DE) blocks signal transduction pathways implicated in the proliferation and survival of cancer cells [4]. Four phase I studies have shown that gefitinib is generally well tolerated, with evidence of antitumor activity in a range of tumors including NSCLC [5-8]. Observations and pharmacokinetic data from these trials identified two doses for further study: gefitinib 250 mg/d is higher than the lowest dose at which clinical response was seen, and 500 mg/d is the highest dose level to be tolerated long-term by most patients. Two large phase II gefitinib monotherapy studies (Iressa Dose Evaluation in Advanced Lung Cancer [IDEAL] 1 and 2) in patients with pretreated advanced NSCLC further confirmed that this agent was generally well tolerated and produced durable, clinically significant antitumor activity (response rates for gefitinib 250 mg/d were 18.4% and 11.8% for IDEAL 1 and 2, respectively), with improvement in disease-related symptoms observed in approximately 40% of symptomatic patients [9-11]. These response rates for patients receiving second-line and higher therapy were encouraging, particularly when considered in the context of the retrospective analysis by Massarelli et al [12], in which the response rate declined with each line of therapy (second line, 16.3%; third line, 2.3%). The most frequent drug-related adverse events observed in these two trials were skin rash and diarrhea, which were generally mild (grade 1 and 2). The results of randomized studies are awaited.

There is a strong rationale for combining gefitinib with standard chemotherapy agents. In preclinical studies, gefitinib enhanced the efficacy of cytotoxic agents against a range of human tumor xenografts, including lung cancer, regardless of EGFR expression [13,14]. A small phase I study of 24 patients with chemotherapy-naïve, advanced NSCLC showed that gefitinib in combination with paclitaxel and carboplatin was well tolerated, with no clinically significant pharmacokinetic drug-drug interactions [15]. Together, these preclinical data, data from gefitinib single-agent trials, and the favorable tolerability data from the phase I trial of this combination supported phase III investigation.

The Iressa NSCLC Trial Assessing Combination Treatment (INTACT) 2 was a randomized, placebo-controlled trial of paclitaxel and carboplatin with or without gefitinib in chemotherapy-naive patients with advanced NSCLC. This global multicenter study was conducted mainly (80%) in the United States; INTACT 1, a parallel global trial that evaluated the combination of gefitinib with gemcitabine and cisplatin, was conducted mainly in Europe. The results of INTACT 1 are reported elsewhere [16]. The primary objective of INTACT 2 was to determine overall survival, and the secondary end point was time to progression. Additional end points included objective response rate, disease-related symptom and quality-of-life outcomes, and adverse-event profiling.

PATIENTS AND METHODS

Eligibility Criteria

Patients were assessed by physical examination and history to ensure that eligibility criteria were met. Entry criteria included histologically confirmed NSCLC (cytologic specimens obtained by brushing, washing, or needle aspiration of a defined lesion were acceptable), unresectable stage III or IV disease, no prior chemotherapy, age $\geq$ 18 years, and performance status 0 to 2. Exclusion criteria included the presence of mixed NSCLC or small-cell lung cancer, brain metastases that were newly diagnosed or had not been treated with surgery or radiation, previously treated CNS metastases or spinal-cord compression in the absence of clinically stable disease, less than 2 weeks since radiotherapy, unresolved toxicity from prior radiotherapy or incomplete healing from

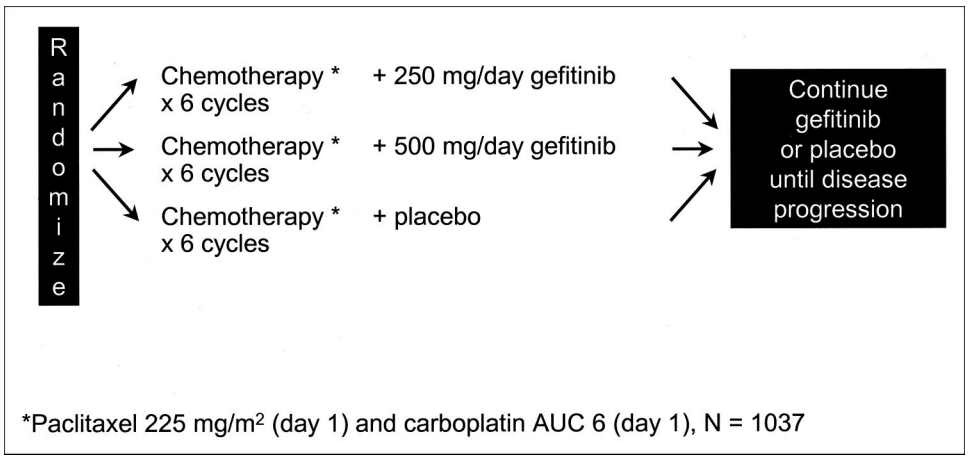

Fig 1. INTACT 2 trial schema. AUC, area under concentration-time curve.

Table 1. Patient Characteristics

	Gefitinib 500 mg/d (n = 347)	Gefitinib 250 mg/d (n = 345)	Placebo (n = 345)
Sex, %			
Female	40.1	42.3	38.6
Male	59.9	57.7	61.4
Age, years			
Median	62	61	63
Range	26–82	27–86	31–85
Disease stage, %*			
IIIa	2.6	2.3	3.8
IIIb	15.3	16.2	17.1
Without pleural effusion	3.5	3.2	5.2
With pleural effusion	11.8	13.0	11.9
IV	81.8	81.2	78.3
WHO performance status, %*			
0	34.6	33.0	38.6
1	51.9	56.5	51.9
2	13.3	10.4	9.3
Weight loss in previous 6 months, %*			
≤ 5%	59.1	62.6	60.9
> 5%	39.5	37.1	38.3
Disease measurability, %*			
Measurable	93.9	91.3	88.4
Nonmeasurable	5.8	7.8	11.0
Histology, %*			
Squamous	16.7	20.3	19.4
Adenocarcinoma	57.9	55.7	51.9
Adenosquamous	2.9	2.3	1.7
Bronchoalveolar	2.9	2.9	3.2
Unspecified NSCLC	11.5	9.6	11.3
Large cell	7.2	8.7	11.0
Race, %			
White	88.5	90.4	91.9
Black	7.5	4.1	5.2
Other	4.0	5.5	2.9

Abbreviation: NSCLC, non–small-cell lung cancer.
*Information was not available for all patients.

surgery, evidence of severe systemic disease, greater than trace blood or protein on repeat urinalysis, absolute neutrophil count less than 2,000/μL, WBCs less than 4,000/μL, platelets less than 100,000/μL, serum bilirubin greater than 1.25 times the upper limit of reference range (ULRR); ALT or AST greater than 2.5 times ULRR (> five times ULRR in the presence of liver metastases), serum creatinine greater than 1.5 times ULRR, pregnancy or breast-feeding, and hypersensitivity to mannitol, corticosteroids, H_2-antagonists, antihistamines, or agents formulated with polyoxyethylated castor oil.

All patients gave written informed consent and approval was obtained from the ethics committee at each trial center. The study followed the Declaration of Helsinki [17] and good clinical practice guidelines.

Trial Design

All patients received chemotherapy (intravenous paclitaxel 225 mg/m^2 over 3 hours on day 1 of a 3-week cycle immediately followed by intravenous carboplatin area under concentration/time curve [18] of 6 mg/min/mL over 15 to 30 minutes on day 1) and were randomized to receive either oral gefitinib at 250 or 500 mg/d or daily oral placebo (Fig 1). Chemotherapy was continued for six cycles in the absence of disease progression. Thereafter, patients were maintained on gefitinib or placebo until disease progression or drug intolerance.

Before randomization, patients were stratified according to weight loss in the previous 6 months (≤ 5% *v* > 5%), disease stage (III *v* IV), performance status (0 or 1 *v* 2), and the presence of measurable disease (yes *v* no).

Statistical Analysis

The trial was governed by a steering committee of INTACT principal investigators. The ongoing safety review and interim analyses were conducted by an Independent Data Monitoring Committee. The first interim analysis was for safety, to rule out a detrimental survival effect for gefitinib early in the trial.

Gefitinib was compared with placebo on an intent-to-treat basis with respect to overall survival. The study was designed to have 90% power for a two-sided overall significance level test of the hypothesis that gefitinib increases survival relative to placebo, given a hazard ratio of 1.33. Assuming a 1-year survival rate of 30% in the placebo arm, in line with the data available at the time of

protocol writing, this hazard ratio equates to an increase in median survival of 2.3 months for both gefitinib arms. The final analysis of overall survival was planned to include 750 events. Based on the study design assumptions, 1,029 patients were required.

At the final analysis, an adaptive survival analysis procedure was used that tested either for a positive or negative gefitinib dose-response relationship, based on prospective criteria applied to the observed data. A survival trend test (global ordered log-rank [GOLrank] test), in which the hypothesis was no effect versus the specific ordering of placebo, gefitinib 250 mg/d, and gefitinib 500 mg/d, was used for a positive dose-response, whereas pairwise log-rank tests would be used for a mixed dose-response [19]. To preserve an overall two-sided 5% significance level, and to account for the use of a survival trend test at the second interim analysis, simulations with the adaptive procedure were used to calculate a nominal significance level of 4.4% for the final analysis. According to prospective criteria for the adaptive procedure, the final analysis used a survival trend test to compare survival between the treatment arms.

A posthoc multivariate analysis with eight prespecified prognostic factors at trial entry (disease stage III *v* IV; performance status 0 or 1 *v* 2; weight loss in prior 6 months $\leq$ 5% *v* $>$ 5%; sex; histology; presence or absence of metastases to bone, liver, or brain) was performed to assess which variables were predictive of improved survival.

In a posthoc subgroup analysis, stratification and prognostic factors (disease stage III *v* IV; performance status 0 or 1 *v* 2; weight loss in prior 6 months $\leq$ 5% *v* $>$ 5%; presence or absence of metastases to bone, liver, or brain) and subgroups of sex, time on chemotherapy, and histology were analyzed in a univariate model. An unadjusted Cox proportional hazard test was applied to the overall survival data for each subgroup to estimate the hazard ratio and 95% CI for the treatment comparisons of gefitinib 250 or 500 mg/d versus placebo.

Assessments

Overall survival and time to progression were assessed from the date of randomization to the date of death (any cause) and the date of objective disease progression (death was considered a progression event in patients who died before disease progression), respectively. Patients without documented death or objective progression at the time of the final analysis were censored at the date last known to be alive or their last objective tumor assessment, respectively.

Tumor response was evaluated according to Response Evaluation Criteria In Solid Tumors, the revised version of the International Union Against Cancer/WHO criteria [20].

During the trial, and for 30 days after the last dose of gefitinib or placebo, patients were monitored for adverse events, graded according to the National Cancer Institute Common Toxicity Criteria (CTC) version 2.0. Hematology and biochemistry assessments were performed $\leq$ 7 days before the date of randomization and at each clinic visit. Analysis of other end points, such as symptom improvement rate, quality of life, and correlation of EGFR with survival, is ongoing and will be reported separately.

RESULTS

Patients

In total, 1,037 patients were recruited between May 2000 and April 2001, approximately 80% of whom were in the United States. The baseline characteristics of the patients were similar in each of the three treatment groups (Table 1). Most patients (approximately 80%) had metastatic stage IV disease, and more than 50% of patients in each group had adenocarcinoma. Approximately 20% of patients in each of the treatment groups are confirmed to have continued receiving chemotherapy after withdrawal from the study.

Efficacy

At each interim analysis, the Independent Data Monitoring Committee made recommendations to continue the trial. A total of 725 events (246, 232, and 247 events for gefitinib 500 mg/d, gefitinib 250 mg/d, and placebo, respectively) were observed for survival and 637 events (178, 215, and 244 events, respectively) for time to progression, with a minimum follow-up of 12 months for survival and 6 months for all other end points.

At the final analysis, neither dose of gefitinib improved overall survival when added to paclitaxel and carboplatin compared with paclitaxel and carboplatin plus placebo (GOLrank $P = .6385$). Median survival was 8.7, 9.8, and 9.9 months in the gefitinib 500 mg/d, gefitinib 250 mg/d, and placebo arms, respectively (Fig 2A). The 1-year survival

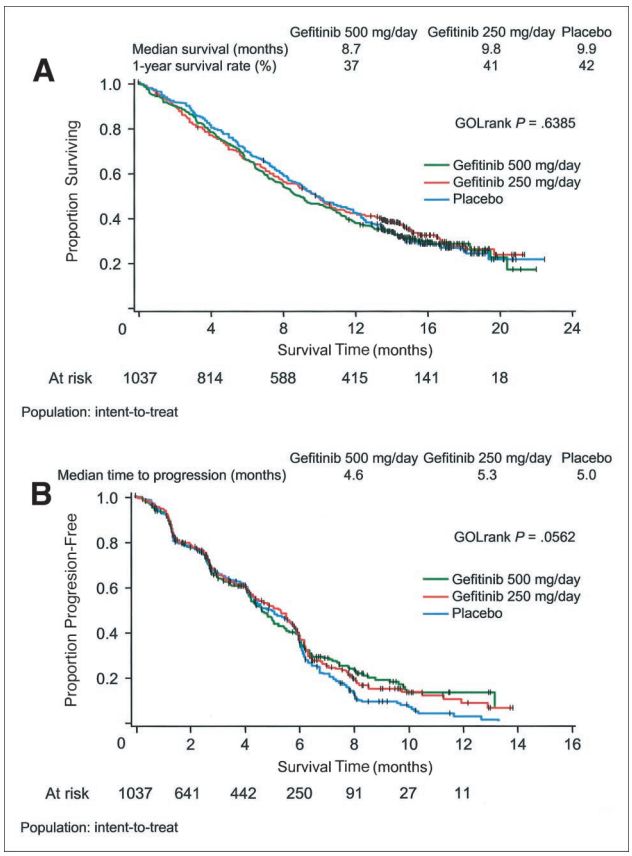

Fig 2. Kaplan-Meier estimates of (A) overall survival and (B) time to progression. GOLrank, global ordered log-rank test.

Table 2. Unadjusted Cox Proportional Hazard Model: Survival by Subgroup (ITT population)

Factor	Placebo *v* Gefitinib 250 mg/d			Placebo *v* Gefitinib 500 mg/d		
	Hazard Ratio*	95% CI	*P*	Hazard Ratio*	95% CI	*P*
Sex						
Male	1.074	0.858 to 1.345	.531	1.112	0.891 to 1.388	.349
Female	0.945	0.700 to 1.277	.714	0.761	0.567 to 1.023	.070
Disease stage						
III	0.986	0.651 to 1.492	.947	1.312	0.845 to 2.036	.226
IV	1.060	0.868 to 1.294	.571	0.917	0.754 to 1.114	.381
Performance status						
0 or 1	1.047	0.864 to 1.269	.641	1.003	0.827 to 1.215	.980
2	0.972	0.587 to 1.610	.911	0.903	0.567 to 1.439	.668
Weight loss in the 6 months prior to entry						
≤ 5%	1.034	0.814 to 1.314	.786	0.974	0.767 to 1.237	.829
> 5%	1.012	0.771 to 1.328	.933	0.951	0.728 to 1.243	.714
Histology type						
Adenocarcinoma, including bronchoalveolar carcinoma	1.156	0.905 to 1.476	.247	1.030	0.812 to 1.306	.808
Other	0.919	0.642 to 1.315	.642	0.738	0.523 to 1.042	.084
Metastases						
Bone	0.835	0.595 to 1.171	.296	0.946	0.685 to 1.307	.737
Liver	1.028	0.703 to 1.503	.887	0.899	0.617 to 1.311	.580
Brain	1.727	0.727 to 4.104	.216	0.673	0.335 to 1.352	.266

Abbreviation: ITT, intention to treat.
*A hazard ratio greater than 1 indicates that patients who received 250 or 500 mg/d of gefitinib live longer than those given placebo. A hazard ratio less than 1 indicates that patients who received placebo live longer than those given 250 or 500 mg/d of gefitinib.

rates were 37%, 41%, and 42%, respectively. Similarly, there was no statistically significant difference between the three groups in median time to progression (4.6, 5.3, and 5.0 months, respectively; GOLrank $P = .0562$; Fig 2B).

In the posthoc multivariate analysis, performance status of 2, weight loss, and bone and liver metastases were significant ($P < .05$) predictors of worse survival outcome. Survival differences were also seen for sex and brain metastases. For the posthoc univariate analysis, generally similar patterns were observed in each of the subgroup analyses, showing no overall difference between treatment groups ($P > .05$, not significant; Table 2). There was no survival advantage in any of the subgroups when gefitinib at any dose was added to chemotherapy. However, there was a trend toward improved survival in the subgroup of patients with adenocarcinoma who had received chemotherapy for ≥ 90 days (patients would have received at least the median number of chemotherapy cycles) in the gefitinib 250 mg/d arm ($P = .05$; Fig 3), suggesting a possible effect of gefitinib monotherapy as maintenance therapy. Although this trend continued for other subgroups (Table 3), the numbers were too small to yield statistical significance.

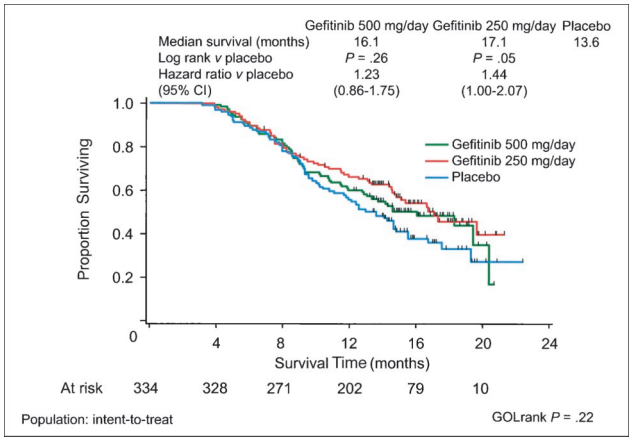

Fig 3. Subset analysis of patients with adenocarcinoma who received ≥ 90 days of chemotherapy. GOLrank, global ordered log-rank test.

Complete responses were rare, observed in 0.6%, 2.6%, and 1.2% of patients in the gefitinib 500 mg/d, gefitinib 250 mg/d, and placebo arms, respectively, and overall response rates were 30.0%, 30.4%, and 28.7%, respectively, demonstrating no statistically significant efficacy difference between treatment arms.

Duration of Therapy, Dose Adherence, and Dose-Intensity

Patients receiving gefitinib 250 mg/d or placebo had a longer duration of therapy than those receiving gefitinib 500 mg/d (Table 4). Similarly, the number of gefitinib dose interruptions and reductions was highest in the gefitinib 500 mg/d arm and similar in the gefitinib 250 mg/d and placebo arms. There was a high overall adherence to gefitinib, and the median dose-intensity for both paclitaxel and carboplatin was similar in all treatment arms (Table 4).

Table 3. Landmark Analyses

Chemotherapy	No. of Patients	Median Survival (months)		
		Gefitinib 500 mg/d	Gefitinib 250 mg/d	Placebo
≥ 90 days	599	14.1	14.9	13.0
≥ 90 days + adenocarcinoma	334	16.1	17.1	13.6
≥ 90 days + stage IV disease	458	12.0	15.1	12.6
≥ 90 days + adenocarcinoma + stage IV disease	260	13.7	19.7	12.5

Safety and Tolerability

Most adverse events occurred during combination treatment and many were attributed to chemotherapy. The safety profile of gefitinib from the monotherapy phase of the trial was similar to that seen in the phase II program. The most common adverse events were gastrointestinal, skin-related, and hematologic in nature. The incidence of acne and rash by grade is shown in Table 5; most of these events were mild (grade 1 or 2). Hematologic adverse events occurred with similar incidence in all three treatment groups, consistent with the toxicity profile of chemotherapy. Gefitinib did not seem to exacerbate these toxicities. Interstitial lung disease (ILD)–type events were experienced by 1.5%, 2.1% and 0.9% of patients in the gefitinib 500 mg/d, gefitinib 250 mg/d, and placebo arms, respectively, and the incidence of dyspnea and other pulmonary adverse events such as cough and pneumonia were generally similar across treatment arms (Table 6). For those adverse events considered to be drug-related (possibly related to gefitinib or placebo), there was a gefitinib dose-response relationship for skin and gastrointestinal events (Table 7). The most frequent grade 3 or 4 drug-related adverse events were diarrhea and rash, which occurred at a higher incidence in the gefitinib 500 mg/d arm than in the gefitinib 250 mg/d or placebo arms (Table 7). Statistical analysis of prespecified adverse events during the chemotherapy phase revealed no difference between treatment arms except for diarrhea ($P <$ .0001 for gefitinib 500 mg/d *v* gefitinib 250 mg/d or placebo; $P = .0011$ for gefitinib 250 mg/d *v* placebo), defined skin events ($P = .0001$ for gefitinib 500 mg/d *v* gefitinib 250 mg/d; $P < .0001$ for gefitinib 500 mg/d or gefitinib 250 mg/d *v* placebo), and CTC grade 3 and 4 infectious events (predominantly sepsis and febrile neutropenia, rather than any specific or localized infections; $P =$ not significant for gefitinib 500 mg/d *v* gefitinib 250 mg/d; $P = .0099$ for gefitinib 500 mg/d *v* placebo; $P = .022$ for gefitinib 250 mg/d *v* placebo). No adjustments were made to the *P* values in these analyses to take account of the multiple comparisons.

Posthoc analyses were performed to assess the survival status for patients with specific rash and diarrhea events. The first analysis was performed in a subgroup of patients with any CTC grade event with Coding Symbols for a Thesaurus of Adverse Reaction Terms of acne, rash, or dry skin. The second analysis was performed in a subgroup of patients with CTC grade ≥ 2 events (specifically acne, rash, dry skin, and diarrhea). Neither posthoc analysis showed a difference in overall survival between the three treatment groups.

Only six deaths were considered to be drug-related: three patients in the gefitinib 500 mg/d arm (sudden death, intestinal obstruction, and dehydration plus kidney failure); one in the gefitinib 250 mg/d arm (pulmonary embolus); and two in the placebo arm (sepsis and cerebral vascular accident). The type of adverse events leading to withdrawal were similar in all three treatment groups, the most common being diarrhea. Fewer patients discontinued therapy because of adverse events (any cause) in the ge-

Table 4. Duration of Therapy, Dose Adherence, and Dose-Intensity

	Gefitinib 500 mg/d (n = 342)	Gefitinib 250 mg/d (n = 342)	Placebo (n = 341)
Gefitinib			
Median duration of gefitinib/placebo therapy, days	99	129	138
Dose interruption, %*	55.0	26.3	20.5
Dose reduction, %*	28.9	8.2	3.2
Median dose adherence, %	92.2	98.9	99.5
Chemotherapy			
Median no. of chemotherapy cycles	5	5	6
Paclitaxel median dose-intensity, %	95.3	96.0	96.1
Carboplatin median dose-intensity, %	85.8	87.4	88.5

NOTE. Data are for population assessable for safety.
*Percentage of patients with at least one dose interruption or reduction.

Table 5. Skin Reactions by Grade

	% of Patients		
	Gefitinib 500 mg/d (n = 342)	Gefitinib 250 mg/d (n = 342)	Placebo (n = 341)
Rash			
None	26.0	40.0	55.1
Grade 1	32.2	40.4	32.0
Grade 2	29.8	15.8	11.4
Grade 3	11.1	3.8	1.5
Grade 4	0.9	0	0
Acne			
None	73.1	79.0	90.6
Grade 1	10.5	14.0	7.3
Grade 2	11.4	6.1	2.1
Grade 3	4.4	0.9	0
Grade 4	0.6	0	0
Rash or acne			
None	20.8	33.6	51.9
Grade 1	33.0	42.1	33.7
Grade 2	31.6	19.6	12.9
Grade 3	13.7	4.7	1.5
Grade 4	0.9	0	0

fitinib 250 mg/d and placebo groups (10.5% and 7.9%, respectively) than in the gefitinib 500 mg/d group (22.5%).

DISCUSSION

This large, randomized, placebo-controlled trial examined the efficacy and safety of gefitinib in combination with paclitaxel and carboplatin for the front-line therapy of advanced NSCLC. The data from 1,037 patients demonstrate that combination of conventional chemotherapy with gefitinib did not improve patient survival, disease-free survival, or response rate compared with chemotherapy given alone. Results with gefitinib 250 mg/d were similar to those in the placebo arm, whereas gefitinib 500 mg/d tended toward a worse outcome, although it was not statistically different from placebo. Median survival was 8.7, 9.8, and 9.9 months in the gefitinib 500 mg/d, gefitinib 250 mg/d, and placebo arms, respectively. These results are disappointing and surprising in view of recent results obtained with the phase II studies of single-agent gefitinib in recurrent NSCLC (IDEAL 1 and 2). Tumor response rates of 11.8% to 18.4% and a clinically meaningful symptom improvement of approximately 40% were reported [9,11]. However, in contrast to the current study in chemotherapy-naive patients, the phase II studies recruited patients with recurrent or refractory disease after prior chemotherapy regimens that included platinum. It has yet to be determined whether this difference in patient population alone influenced the lack of additional response seen in our study. It could be speculated that recurrent NSCLC uses EGFR ligands as potential survival factors after platinum-based chemotherapy, as it has been reported that EGF stimulates production of the survival factor vascular endothelial growth factor [21,22]. Recent results show that two phase III trials of first-line erlotinib in combination with standard chemotherapy in patients with metastatic NSCLC did not meet their primary end point of improving overall survival.

Table 6. Pulmonary Adverse Events

	Gefitinib 500 mg/d (n = 342)	Gefitinib 250 mg/d (n = 342)	Placebo (n = 341)
Dyspnea, %	34.2	36.5	32.6
Cough, %	26.6	27.8	24.3
Pneumonia, %	8.5	8.2	8.5
ILD event, n	5	7	3

Abbreviation: ILD, interstitial lung disease.

The current results are also surprising given the striking results reported for gefitinib in combination with chemotherapy in animal models [13,14]. Given our findings, the relevance of animal models to human cancers should be carefully examined, as experimental preclinical results frequently do not translate to the clinic. One factor is the lower doses of chemotherapy agents often used in animal models to observe a synergy with biologic therapies. We used the maximum therapeutic dose of carboplatin and paclitaxel in this human trial, which might have negated this effect. Another limitation is related to tumor implantation in the animal models. Rather than orthotopic tumors, most researchers use subcutaneous ectopic tumor implants, which are devoid of interaction with the true microenvironment of lung cells, and this could specifically alter tumor growth in vivo and perhaps the response to these agents [23,24]. Additionally, many of these cells are implanted only a short time before the start of therapy, which is, of course, much different from the human situation. These unrealistic growth patterns may also alter the response to therapy. Interestingly, the subset analysis of adenocarcinoma patients who received $\geq$ 90 days of chemotherapy suggests that patients receiving gefitinib 250 mg/d who completed therapy had some long-term survival benefits, indicating that gefitinib might be effective as a cytostatic agent in humans, maintaining tumor regression after chemotherapy. This may be due to the ability of gefitinib to block EGFR-dependent survival pathways or possibly due to enhancement of apoptosis. However, this was not seen to the same significant extent in INTACT 1 [16]. These analyses were done posthoc and suffer from selection factors. Furthermore, as many analyses were performed for different subgroups, it is possible that observed effects could have appeared by chance alone. Perhaps the best use of gefitinib in vivo will be in sequence with chemotherapy. This hypothesis can be tested in randomized trials, and plans are underway to initiate such trials. Several options exist, in-

Table 7. Common Drug-Related* Adverse Events (% of patients)

	% of Patients					
	Gefitinib 500 mg/d (n = 342)		Gefitinib 250 mg/d (n = 342)		Placebo (n = 341)	
	All	Grade 3 or 4	All	Grade 3 or 4	All	Grade 3 or 4
Diarrhea	69.3	25.4	58.2	9.9	29.3	2.9
Rash	67.3	11.7	54.4	3.2	37.5	1.5
Acne	26.3	5.0	19.9	0.9	7.3	0
Dry skin	25.7	1.5	15.2	0.3	4.4	0
Pruritus	20.5	1.8	15.2	0.6	12.6	0.3
Nausea	18.7	4.1	19.3	1.8	14.7	2.1
Vomiting	12.9	2.9	11.7	2.0	9.4	2.3
Anorexia	11.7	0.6	7.0	0.6	6.2	0.3
Asthenia	11.1	2.3	13.5	0.3	10.3	1.2
Dehydration	9.9	5.0	3.8	1.8	2.9	1.8
Neutropenia	7.0	6.1	7.9	6.7	5.9	5.9
Anemia	6.7	1.2	6.4	0.6	2.6	0.6
Neuropathy	4.1	0.9	5.3	0.3	5.9	0.9
Leukopenia	3.2	2.3	5.3	2.0	3.8	2.1
Conjunctivitis	6.4	0.6	5.3	0	3.2	0
Alopecia	1.5	0	4.7	0	4.7	0
Dyspnea	0.9	0.3	0.9	0.6	1.5	0.3

*Possibly related to gefitinib/placebo.

cluding first-line gefitinib followed by chemotherapy, gefitinib maintenance therapy after response to chemotherapy or radiotherapy, or adjuvant gefitinib after surgery or radiotherapy for early-stage disease.

This trial was the first placebo-controlled study to address the question of gefitinib safety, and it confirms the safety profile from phase I and II monotherapy trials. Diarrhea and skin toxicity were milder and less frequently reported in the 250 mg/d dose group than in the 500 mg/d group. The frequency of other gastrointestinal side effects was relatively low and similar to the placebo arm. With the exception of mild-to-moderate diarrhea and skin-related events, the gefitinib 250 mg/d arm exhibited a safety profile similar to the placebo arm. Recently, ILD has been reported for four of 18 patients treated with gefitinib for NSCLC, two of whom died [25]. The same incidence was not seen in this randomized controlled study, in which the incidence of ILD-type events was similar in all treatment arms. The favorable tolerability of gefitinib is further supported by the high overall dose adherence. In addition, no change of the expected chemotherapy-related toxicity was observed in the gefitinib-treated arms. Other than dose-response effects, no predisposition factors for gefitinib toxicity were identified, and it can be concluded that gefitinib 250 mg/d has an acceptable safety profile when administered alone or in combination with chemotherapy. Similar results were seen in the INTACT 1 study [16].

Another possible explanation for the lack of a survival difference seen in this study is that patients were not selected on entry for sensitivity to the study agent (in large part because a sensitivity assay does not yet exist). High expression of EGFR has been associated with lower relapse-free and overall survival rates in several malignancies in retrospective studies [26]. However, sensitivity to anti-EGFR therapy does not seem to be correlated with expression of this receptor [27], and conflicting results regarding the relationship between receptor expression and the efficacy of gefitinib have been reported [14,28-31]. It is possible that only patients with upregulated signal transduction pathways along the EGFR axis, such as the Akt pathway, might benefit. Patient selection was important in the use of trastuzumab in metastatic breast cancer, where a positive result with chemotherapy was seen in the subgroup of patients who had significant overexpression of the target [32].

At this time there is no standard method to detect EGFR, HER2, and their phosphorylated forms. Evaluation of the biology of NSCLC tumors treated with gefitinib is currently underway to identify the targets and mechanisms of response and resistance to therapy. Results from the 480 samples collected from patients enrolled in this study will be provided in a separate report. Exploratory analysis of tumor biopsies taken from patients in the IDEAL 1 and 2 trials used a reproducible immunohistochemical assay to estimate the correlation of EGFR membrane staining intensity (no, weak, moderate, or strong staining [0, 1+, 2+, 3+, respectively]) with the probability of objective tumor response or symptom improvement, with the null hypothesis that membrane staining intensity is not predictive of clinical outcome [33,34]. The mean proportion of cells staining 2+ or 3+ was 31.3% for patients with response and 37.5%

for those without response. Furthermore, in both IDEAL trials, five (15%) of 34 patients had response with less than 10% detectable staining. The mean percentage with 3+ staining was 32.1% for patients with and 22.8% for patients without symptom improvement. Therefore, the results of this analysis did not reveal a consistent association between EGFR membrane staining and either objective response or symptom improvement.

Although the current INTACT 2 study did not show superior efficacy when gefitinib was added to paclitaxel and carboplatin, the overall safety profile of gefitinib was confirmed. These data contribute to a better understanding of the optimal use of gefitinib as monotherapy in refractory disease and potentially in sequence with chemotherapy for previously untreated patients with NSCLC.

Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant within the last 2 years: Giuseppe Giaccone, AstraZeneca; Roy S. Herbst, AstraZeneca; Christian Manegold, AstraZeneca; Giorgio Scagliotti, AstraZeneca; Joan Schiller, AstraZeneca; Ronald Natale, AstraZeneca; Vincent Miller, AstraZeneca; David H. Johnson, AstraZeneca. Received more than $2,000 per year from a company for either of the last 2 years: Ronald Natale, AstraZeneca; Vincent Miller, AstraZeneca.

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